REMARKS

I. Status of the Claims

Claims 1 through 9 are pending in the application. Claim 1 is an independent claim. Claims 1, 6 and 9 have been amended to address the rejections made in the Office Action under 35 U.S.C. § 112, second paragraph. Reconsideration of the outstanding rejections and objections is respectfully requested in view of the foregoing amendment and these remarks.

II. Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 1-2, 6 and 8-9 have been rejected under 35 U.S.C. § 112, second paragraph. Claim 1 has been amended to further clarify that the compound of formula (I) is administered orally, and that the administration with food increases the bioavailability of the compound.

With respect to Claim 2, ospemifene is the (Z) isomer of the compound of formula (I). Therefore, Claim 2 is a proper dependent claim, further limiting the base claim, and no amendment has been made. In claim 6, "capable of" has been deleted in response to Examiner's objection.

To clarify that claim 9 further defines "the symptoms" recited in claim 8, from which it depends, claim 9 now recites symptoms related to atrophy. Note that skin, epithelial or mucosal atrophy is a separate and distinct indication from osteoporosis. Both atrophy and osteoporosis are conditions that may be treated with ospemifene, and in fact patents have been obtained on both treatments. As pointed out in the specification at page 5, paragraph [0021], urinary symptoms and vaginal symptoms are associated with atrophy. Thus, Claim 9 is a proper dependent claim.

III. Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 7 and 8 have been rejected under 35 U.S.C. § 112, first paragraph, for alleged lack of enablement. With respect to claim 7, the Examiner appears to question altogether whether osteoporosis can be prevented with drugs. With respect to claim 8, the Office Action suggests that skin atrophy cannot be prevented. Applicants respectfully traverse.

All of the art of record, including the art cited in the Office Action, teaches that prevention of osteoporosis, along with treatment of osteoporosis, is a legitimate clinical target. U.S. Patent No. 5,912,273, claims "a dosage formulation suitable for use in the prevention or treatment of osteoporosis" (emphasis added), and the formula in claim 1 of the '273 patent includes ospemifene. Biskobing, at page 112, notes that raloxifene (another SERM) is approved by the FDA for prevention and treatment of postmenopausal osteoporosis, and the FDA has established guidelines to conduct clinical studies to prove the efficacy of the study drugs. Thus one of ordinary skill in the art recognizes that a SERM may be a candidate for both prevention and treatment of osteoporosis, for example, where it is found to be selective in bone tissue that is generally subject to estrogens (as is the case with ospemifene), because it is likely to maintain or improve bone density. Beyond that, the efficacy of drugs is a matter for the FDA, as clinical studies are not initiated until after a patent application has been filed, and the inquiry into efficacy well beyond the enablement standard implicated under 35 U.S.C. § 112.

Moreover, the Office Action seems to suggest that there is a very high standard for a claim to "prevention," as opposed to "treatment." Clearly a drug approved

for prevention and treatment of osteoporosis, such as raloxifene (sold under the tradename Evista), is not presumed to be 100% effective. A woman taking that drug for prevention is not assured that she will never suffer from osteoporosis. Rather, "prevention" in this context merely means that the disease is treated before it begins, more in the sense of "hinder" or "forestall," which are offered as synonyms for prevent in the dictionary (Webster's Ninth New Collegiate). As an example, take the treatment of osteopeonia (*i.e.* lowered bone mineral density) that has not been diagnosed as osteoporosis. Clearly such treatment would legitimately be considered a prevention of osteoporosis, and would be amply enabled, given the state of the art.

With respect to the claims for prevention and treatment of atrophy, the same considerations apply. The Examiner argues as follows: "Atrophic change in the skin has been noted as a prominent part of the aging process. The only way possible [to prevent atrophy] is to stop aging and that is not possible, therefore how is skin atrophy prevented." (Office Action, page 9). Clearly all that is meant by the use of the word "prevention," in the context of claim 8, is that the drug is administered before the condition has set in, and thereby acts to forestall or hinder atrophy. In that sense, "prevention" is amply enabled, given the state of the art.

In view of the foregoing, the specification is believed to be enabling for the claims to prevention and treatment of osteoporosis, and to the prevention and treatment of atrophy, and the rejection under 35 U.S.C. § 112, first paragraph, should be withdrawn.

IV. Rejections Under 35 U.S.C. § 103

Claims 1 through 9 have been rejected over D.M. Biskobing, *Expert Opinion Invest. Drug* (2003) 12(4) ("Biskobing") in view of WO 97/32574 ("Harkonen") and U.S. Patent No. 6,245,819 ("Halonen").

The important element of the present claims that is not disclosed in any of the references is the use of food to increase the bioavailability of ospemifene. This result is entirely unexpected, and particularly surprising in view of the fact that toremifine, which is a close analog of ospemifene, does not demonstrate increased bioavailability taken with food.

Harkonen says at page 3, lines 9-10: "The compounds of the invention may be administered alone or together with other active compounds." This appears to be the sole reference to "other active compounds." There is no disclosure of taking the compound (ospemifene) with food, no disclosure of increasing the bioavailability of ospemifene with food, and no disclosure of using any "other active compounds" to increase bioavailability, of ospemifene or any other drug.

Assuming, for the sake of argument, that food might be considered an "active compound," as one of ordinary skill in the art would use that term, a proper rejection of the present claims would require a showing that food increases bioavailability of orally administered ospemifene, or at a minimum, a reasonable expectation that administration with food would increase bioavailability.

The opposite is true. As noted in the specification at page 2, a study on the bioavailability of toremifene, M. Antilla, *European Jrnl. Cancer*, 1997 V. 33, Supp. 8, 1144, showed that a close analog of ospemifene did not increase bioavailability when

taken with food. Furthermore, the improved bioavailability of ospemifene taken with food was not earlier achieved in rats, not even using solubles as vehicle. The food interaction is thus not an obvious or inherent feature of ospemifene, as the result can be verified only when the compound is studied clinically. This applies even more to the strength of the effect, which was found to be surprisingly good. Therefore, the expectation in the art, as far as it can be determined from the record of the present patent application, would have been that administration with food would not increase the bioavailability of ospemifene.

Thus, the general assertions at page 11 of the Office Action, even taken at face value (and no references are cited for what is said to be "generally known"), do not render obvious the specific findings claimed herein, *i.e.*, the increased bioavailability achieved by administering the compound with food (presumably arising from secretion of bile acids and salts in the digestive tract).

For the foregoing reasons, the cited prior art does not make obvious a method of increasing the bioavailability of ospemifene by administering the compound with food.

V. Obviousness-Type Double Patenting

All of the claims have been rejected for alleged obviousness-type double patenting over U.S. Applications Nos. 10/783,092, 11/183,185, and 11/201,098, and over U.S. Patent No. 6,984,665. These rejections are respectfully traversed, as none of the applications or the patent applied in the rejections contain any disclosure whatsoever relating to enhancing bioavailability, and the claims of the copending applications and patent cover different indications.

The statement is incorrect at page 12 of the Office Action (referring to the co-pending '092 application) that "Both sets of claims refer to using the same compound ospemifene enhancing bioavailability. . ." (emphasis added). The '092 application does not disclose the administration of food to enhance the bioavailability of ospemifene. It is also incorrect that "the current application claims anticipate the copending application claims," as alleged in the Office Action at page 12, at least because the '092 application claims require treatment of a subject suffering from "increased bone turnover," which element is not found in the present claims.

The '185 application, directed to treating androgen deficiency in men, is directed to treating a different indication in a different population (*i.e.*, androgen deficient males), than is currently claimed, and there is no disclosure in the co-pending '185 patent relating to administration of food to enhance the bioavailability of ospemifene. It is not correct that the "current application claims anticipate the copending application claims," at least because the element of androgen deficiency found in the copending '185 application is not found in the present claims.

The '098 application and the '665 patent are related to treatment or inhibition of urogenital atrophy symptoms and they are based on the same original application. There is no disclosure in either the '098 application or the '665 patent relating to increasing bioavailability by co-administering with food, and of course that element is not recited in the claims of the '098 application or the '665 patent. The present claims are not obvious in view of the '098 application claims or '665 patent claims, at least because the increased bioavailability achieved by taking with food would not have been obvious.

The above amendments and arguments are believed to address the Examiner's rejections under 35 U.S.C. § 112, first and second paragraphs, and under 35 U.S.C. § 103(a). Reconsideration and withdrawal of the rejections in is respectfully requested.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

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